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The clinical relevance of dry powder inhaler performance for drug delivery

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Inhaler resistance;
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Dry powder inhaler

Summary
Background: Although understanding of the scientific basis of aerosol therapy with dry powder inhalers (DPIs) has increased, some misconceptions still persist. These include the beliefs that high resistance inhalers are unsuitable for some patients, that extra fine (<1.0 μm) particles improve peripheral lung deposition and that inhalers with flow rate-independent fine particle fractions (FPFs) produce a more consistent delivered dose to the lungs.
Objectives: This article aims to clarify the complex inter-relationships between inhaler design and resistance, inspiratory flow rate (IFR), FPF, lung deposition and clinical outcomes, as a better understanding may result in a better choice of DPI for individual patients.
Methods: The various factors that determine the delivery of drug particles into the lungs are reviewed. These include aerodynamic particle size distribution, the inspiratory manoeuvre, airway geometry and the three basic principles that determine the site and extent of deposition: inertial impaction, sedimentation and diffusion. DPIs are classed as either dependent or independent of inspiratory flow rate and vary in their internal resistance to inspiration. The effects of these characteristics on drug deposition in the airways are described using data from studies directly comparing currently available inhaler devices.
Results: Clinical experience shows that most patients can use a high resistance DPI effectively, even during exacerbations. Particles in the aerodynamic size range from 1.5–5 μm are shown to be optimal, as particles <1.0 μm are very likely to be exhaled again while those >5 μm may impact on the oropharynx. For DPIs with a constant FPF at all flow rates, less of the delivered dose reaches the central and peripheral lung when the flow rate increases, risking underdosing of the required medication. In contrast, flow rate-dependent inhalers increase their FPF output at higher flow rates, which compensates for the greater impaction on the upper airways as flow rate increases.

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Conclusions: The technical characteristics of different inhalers and the delivery and deposition of the fine particle dose to the lungs may be important additional considerations to help the physician to select the most appropriate device for the individual patient to optimise their treatment.

Introduction

The mainstay of asthma and COPD treatment is via the inhaled route, medication given either to control inflammation (inhaled corticosteroids [ICS]) or to prevent or reverse bronchoconstriction (β_2-agonist or muscarinic antagonist bronchodilators) [1]. A key advantage of the inhaled route of administration is that lower doses of the required drug can be delivered directly to the site of action, resulting in a rapid clinical response with lower potential for risk of systemic adverse effects compared with other routes of administration [2,3].

Increased understanding of the scientific basis of aerosol therapy has led to the development and introduction of many new inhaler devices, including nebulisers, pressurised metered-dose inhalers (pMDIs) and, particularly, dry powder inhalers (DPIs) [3—5]. Approaches including Adaptive Aerosol Delivery (AAD) [6], the AKITA® inhalation system (Activaero, Germany), which controls the breathing manoeuvre [7] and mist inhalers [8], have utilised and exploited new insights into the relationships between factors such as delivered dose, aerosol particle size, inspiratory flow rate (IFR), lung deposition and clinical effects. These insights have also led to a greater awareness of the importance of choice of DPI to suit the individual patient.

Despite these advances in scientific understanding, a number of misconceptions about inhalers have proved very persistent. These include the belief that the optimal flow rate or pressure drop to operate a DPI is 60 L/min or 4 kPa, irrespective of the inhaler design. Other misconceptions include the role of the inhaler's internal resistance, the belief that extra fine particles (with mass median aerodynamic diameter [MMAD] <1 μm) give improved peripheral lung deposition and the belief that inhalers with flow rate independent particle size distribution produce a more consistent delivered dose to the lungs. However, it is beginning to become more widely understood that there is no unique IFR nor pressure drop for optimal use of DPIs. It has also become accepted that higher resistance DPIs can be used effectively, both by COPD patients and by children with an asthma exacerbation, and that they can have several advantages with respect to lung deposition [9—13]. Furthermore, there are good theoretical arguments (with experimental support) to question the benefit of extra fine (<1 μm) particles and flow rate independent aerosol delivery [14]. And finally, lung deposition is not always improved by inhaling faster or more forcefully [15].

Despite the many recent advances and innovations, inhalation therapy is also still associated with poor adherence and many patients have low levels of ability/dexterity or poor breath-to-hand co-ordination and so use their inhaler device incorrectly/ineffectively [16,17]. Even with training, there is a high potential for handling errors, particularly when patients are prescribed different types of inhaler concurrently [18]. Patients also develop strong preferences for specific types of inhalers [19—23], which can have an impact on adherence, particularly if they are switched to a different inhaler type [24]. Switching inhaler device, particularly if the decision is made without consultation, is not recommended [25]. Care should also be taken even when switching among the same type of inhaler — for example a DPI — because different levels of asthma control are achieved even when delivering the same drug [26].

In an effort to reduce the impact of inevitable handling errors, research has been done to produce inhalers that are less dependent on the user for delivery of the optimum dose [27]. In this regard, the performance and specific design characteristics of a DPI, such as the delivered particle size distribution and their internal resistance, have been shown to be important from a clinical perspective, in that they can be modified to minimise the influence of the patient's IFR on the deposition pattern and dose [3,4,16].

The aerosol particle size distribution is known to be one of the main factors influencing the deposition pattern of a drug in the lungs. Historically, the optimal aerodynamic particle size range for deposition in the lung was thought to be <5 μm. The mass fraction of the dose emitted in this size range by a particular inhaler is often referred to as the fine particle fraction (FPF) [28]. The factors determining the FPF generated by a DPI are complex and interrelated [29].

The aims of this article are to clarify the complex interplay between inhaler design and resistance, inspiratory flow manoeuvre, FPF and lung deposition, and to highlight the clinical relevance of this interplay, in terms of effectiveness and outcomes.

Particle size matters

Aerodynamic particle size distribution, in combination with the inspiratory manoeuvre and airway geometry, determines the penetration of drug particles into the airways and deposition on the walls of the airways — and this determines the dose delivered to the target site [13,16,30—33]. Three basic principles are the main determinants of the site and extent of deposition — inertial impaction, sedimentation and (to a lesser extent) diffusion (Fig. 1) [29,30,34]. Particles that are not deposited are exhaled again.

At higher IFRs, most particles >5 μm in diameter will impact on the oropharynx and in the first airway bifurcation. Particles deposited on the oropharynx will be

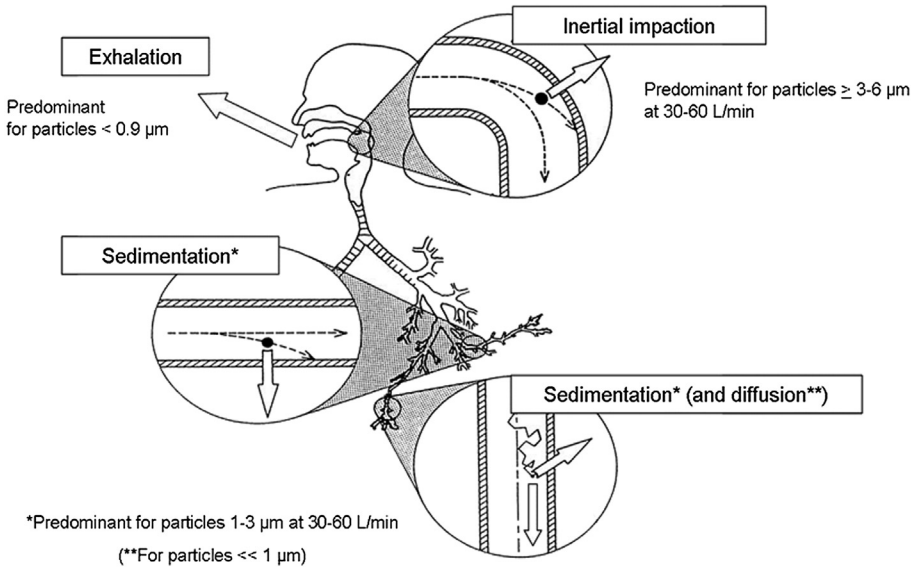

Figure 1 Dominant particle deposition mechanisms in the respiratory tract and effect of particle size on the likelihood of particle penetration and deposition in the airways.

swallowed, potentially contributing to a reduction in efficacy and local oropharyngeal or systemic effects. This was demonstrated by Usmani and colleagues in a randomised, double-blind, placebo-controlled clinical efficacy study in 12 patients with stable mild-to-moderate asthma quantifying deposition with salbutamol aerosols of different particle size (either 1.5, 3 or 6 µm MMAD) at two different flow rates (31 or 67 L/min) [35]. The study demonstrated that deposition fractions of smaller particles (1.5 and 3 µm) in the central and peripheral airways are much higher than those of larger (6 µm) particles, particularly at the higher IFR (Fig. 2) [35]. By extrapolation of data from this study, it can be derived that particles of ≤1 µm have a greater than 40% chance of being exhaled again (both flow rates) due to their low settling velocity, in spite of a short breath-hold period. Bronchodilation (measured as change in forced expiratory volume in 1 s [FEV_1]) following administration of salbutamol significantly decreased with particle size at the higher IFR [35]. Bronchodilation with the 1.5 µm particles was unaffected by IFR. Oropharyngeal deposition increased for all particle sizes at the higher IFR, but this was significantly greater for the larger particles ($p < 0.001$). These findings highlight the dynamic interaction between FPF and IFR and show that this translates into clinical outcomes, i.e. decreased lung deposition and increased oropharyngeal deposition with the higher IFR for large particle sizes results in a reduced bronchodilator effect (Fig. 3) [35]. The Usmani study used monodisperse aerosols (geometric standard deviation <1.22) and similar effects may be expected for aerosols from DPIs with the same MMAD, although they may have slightly wider size distributions.

Although, historically, the optimal aerodynamic particle size range for deposition in the lung was thought to be <5 µm, basic physics, deposition modelling and also *in vivo* deposition studies (e.g. Usmani et al. [35]) indicate that particles smaller than 1.0 µm are undesirable because of their extremely low settling velocity [29]. Because the settling velocity increases with the square of the particle

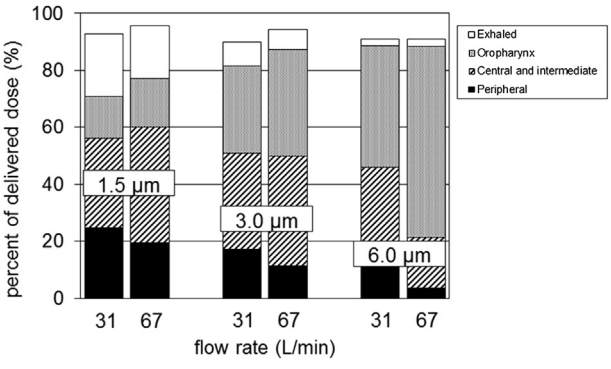

Figure 2 Effect of different inspiratory flow rates (31 or 67 L/min) on lung deposition for three different sizes of particle (1.5, 3.0 or 6.0 µm). Adapted from Usmani et al. (2005) [35].

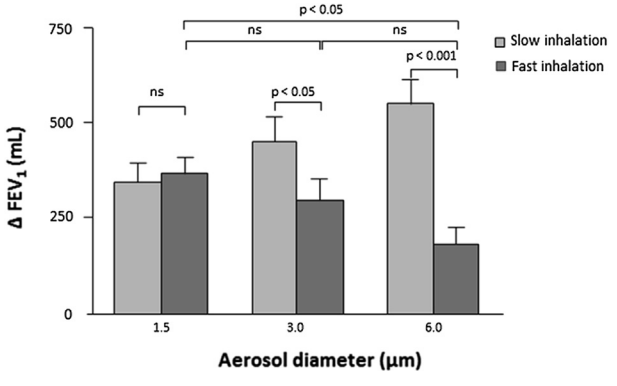

Figure 3 Clinical effects of relationship between inspiratory flow rate (slow [31 L/min] and fast [67 L/min]) and particle size for monodisperse salbutamol aerosols in 12 patients with stable mild-to-moderate asthma [35]. FEV_1, forced expiratory volume in 1 s; ns, not significant.

diameter, the probability of deposition by sedimentation increases rapidly when the particle diameter is increased. For 1.5 μm particles, the time to travel the same distance by falling is 2.25 times shorter than that for 1 μm particles. Also, the chance of inertial deposition in the larger airways increases with increasing diameter, but for particles of approximately 1.5 μm, the oropharyngeal deposition is still low and widely flow rate independent [35]. Therefore, particles of 1.5 μm are more appropriate than <1.0 μm particles and the optimal size range for inhalation seems to be 1.5—5 μm rather than <5 μm.

Drug distribution and concentration in the whole lung

For aerosols from DPIs a reasonably equal distribution (1:1:1) of the total lung dose has been found between the upper (conducting), intermediate (transitional) and lower (peripheral) airways [33,36]. Usmani et al. reported comparable lung distributions for 1.5—3 μm particles inhaled at 30—67 L/min: about two-thirds of total lung dose was deposited in the central plus intermediate and one-third in the peripheral airways (Fig. 2) [35]. This seems to be in fair agreement with the lung distribution from DPIs, although the definitions for central, intermediate and peripheral lung may have been different. However, due to the exponential increase in airway surface area towards the alveoli, so that over 95% of lung surface area is within peripheral airways, the actual concentration for a given dose of drug is significantly higher in the conducting airways than the respiratory airways [33,37]. Differences in average concentration between the conducting and peripheral airways for a 1:1:1 deposition ratio may approach a factor of 100. Deviations from the 1:1:1 ratio in the deposition pattern do not really level out this extreme concentration difference. Even for a ratio of 1:2:3 in favour of a much higher peripheral deposition, which is difficult to achieve in practice with pMDIs and DPIs, the average concentration difference between conducting and peripheral airways is still a factor >30. At the clinical level, this may be highly relevant for drugs that need to particularly target the smaller airways, like corticosteroids, or that need to be more evenly distributed over the entire lung, like antibiotics. Only for bronchodilators has this concentration gradient been considered less relevant so far. Although β_2-agonists and anticholinergics target autonomic receptors on the airway smooth muscle of large and small airways [38], cholinergic activity of the lung is most pronounced in the large airways [39]. Additionally, the amount of smooth muscle gradually decreases from the bronchioles towards the alveoli. Therefore, targeting the larger airways with bronchodilators has been the objective until now. However, several studies are currently underway to investigate the contribution of small airways to asthma and COPD. Recently, it has been proposed that muscarinic receptors may have a much greater role in the pathophysiology of obstructive airway diseases than previously thought [40]. Drugs like tiotropium may potentially inhibit airway inflammation and remodelling [41], whereas for aclidinium an important role in inhibiting fibroblast—myofibroblast transition has been reported, which is a key step in peribronchiolar fibrosis

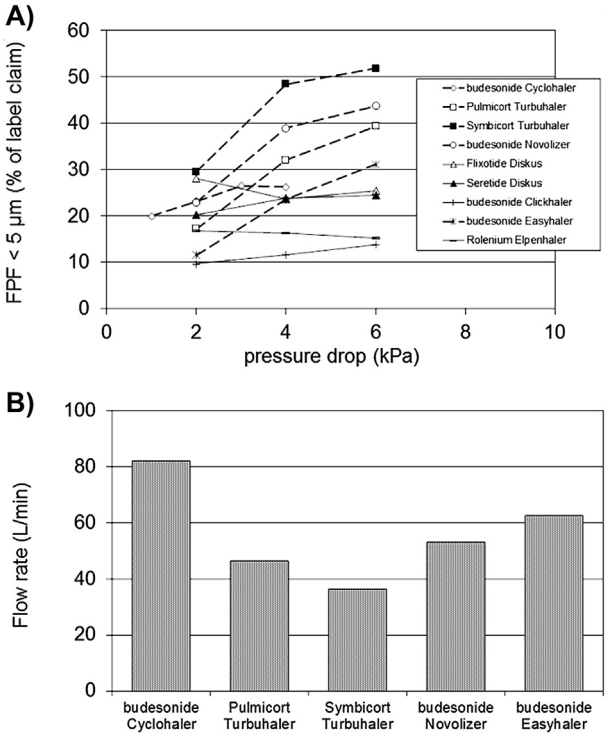

Figure 4 (A) FPF <5 μm by pressure drop across different inhalers and (B) flow rates of various inhalers at which the FPF <5 μm reaches 25% of the label claim. FPF, fine particle fraction.

formation [42]. For these reasons, and also to achieve the desired synergistic effect with ICS, achieving high drug concentrations in the central and peripheral lung may become a future challenge for anticholinergic bronchodilators too. However, a balance must be achieved on particle size, because any drug capable of reaching the alveoli is more likely to be absorbed into the circulation and increase the potential for adverse systemic effects [29].

Flow rate: dependence or independence?

DPIs fall into two main classes — according to whether their FPF output is dependent on, or independent of, the user's IFR [13,16,29,30]. Fig. 4 shows that the percentage of ICS fine particles <5 μm from the (Pulmicort® and Symbicort®) Turbuhaler® and the (Budelin®) Novolizer® inhaler increases at higher IFR, while for the (Seretide®) Diskus®, budesonide Cyclohaler® and (Rolenium®) Elpenhaler®, the percentage is relatively unchanged at different IFRs. It has to be borne in mind that pharmaceutical companies may use different definitions for their label claims, which blurs any performance comparison between devices. Some companies take the weighed drug amount as reference for their label claim whereas others base their label claim instead on the average drug mass released from the mouthpiece.

Whilst an inhaler that produces a consistent percentage of FPF <5 μm independent of the IFR of the patient may appear at first sight to be the best way to ensure reproducible lung deposition, the reality is quite the opposite. An IFR-dependent inhaler produces an increased FPF <5 μm at

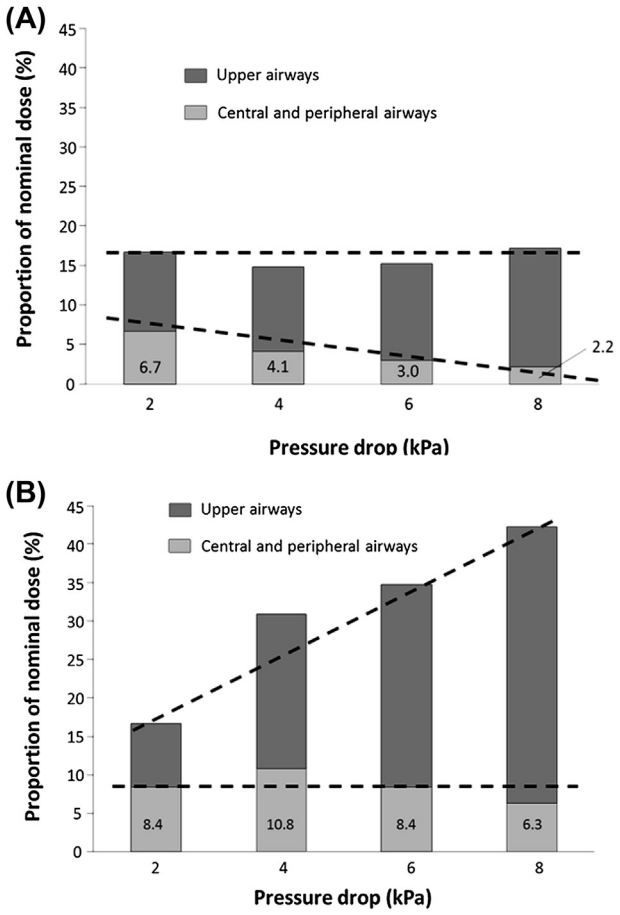

Figure 5 (A) Flow-rate independent inhalers such as Diskus® provide a decreasing dose to the central and peripheral airways as air flow rates (pressure drops) increase, whereas (B) flow-rate dependent inhalers such as Novolizer® maintain their lung deposited dose as air flow rates (and pressure drops) increase [29,30,47].

higher IFR — thus compensating for the shift in deposition towards larger airways due to increased inertial impaction in the oropharynx and first airway bifurcation [29,30,33,36,43—48], which otherwise reduces deposition in the peripheral respiratory airways of the lung at higher IFRs. The compensation should ensure that a relatively constant dose is delivered to where it is needed in the lung regardless of IFR. An example of the difference in lung deposition between constant and IFR-dependent FPF <3 μm is given in Fig. 5 for a comparison between the Diskus® and Novolizer®. Based on the data from an *in vitro* deposition study and by making use of deposition probability equations for particles in the delivered size range, the proportions of this FPF that are deposited in the upper airways and central plus peripheral airways, respectively, can be assessed, as a function of the inspiratory flow rate [30].

IFR-independent inhalers, such as the Diskus®, produce a constant percentage of FPF over a wide range of IFRs, but, at higher IFRs, significantly reduced amounts of the constant fine particle dose actually reach the peripheral airways. The decrease in computed dose reaching the peripheral airways with this IFR-independent inhaler is from 6.7% to 2.2% (Fig. 5A) [30]. Clinically, this means that patients with higher or variable IFRs using IFR-independent inhalers risk under-dosing, particularly with ICS therapies, which, unlike the fast-acting bronchodilators, do not give immediate response feedback to the patient so that they can tell whether their inhalation was insufficient and repeat the procedure if necessary [49]. In contrast, with increasing percentage FPF at higher IFR, the computed peripheral lung dose from the Novolizer® varies from 6.3% to 10.8% (Fig. 5B). These computed values are in good agreement with the data from a lung deposition study in healthy volunteers with radiolabeled budesonide aerosols from the Novolizer® yielding peripheral lung depositions of 6.5% (at 45 L/min), 7.8% (60 L/min) and 8.5% (90 L/min), respectively [36].

Meeting resistance

Drugs for inhalation by DPI in the treatment of asthma and COPD therapy are supplied in one of two forms, either as a so-called adhesive mixture or as soft spherical agglomerates, referred to as pellet formulation (Fig. 6). In adhesive mixture formulations, the micronised drug particles are distributed over the surface of coarse carrier particles by natural adhesion. Pellet formulations may consist of pure

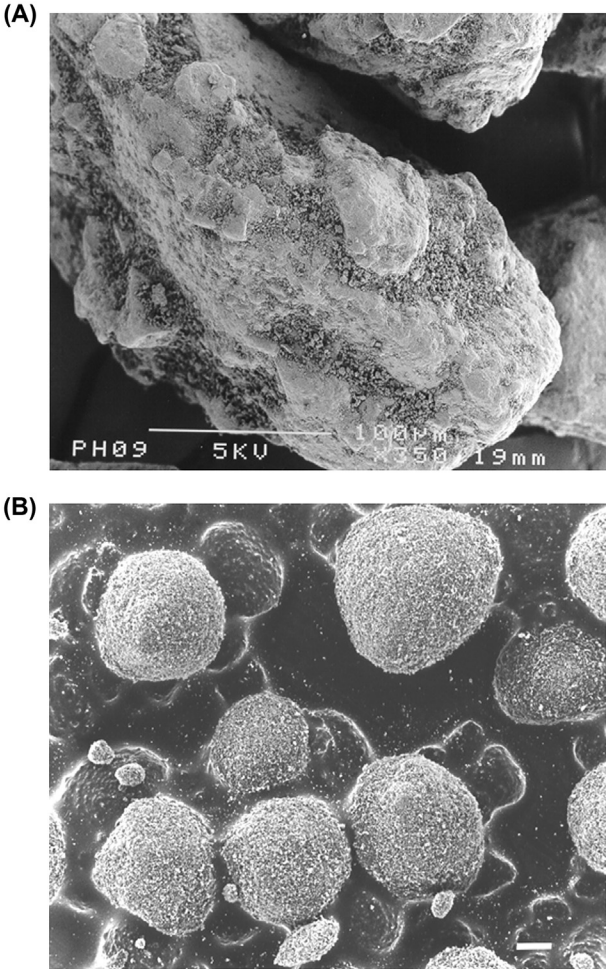

Figure 6 Scanning electron micrographs of (A) adhesive mixture and (B) soft spherical agglomerates/pellets.

Table 1A Review of some corticosteroid (ICS) delivering DPIs.

Inhaler	ICS	Manufacturer	% FPF at 4 kPa		Resistance[a]	FPF as Fu(IFR)	Multi-/single-unit dose
			Defined as	% FPF			
Flixotide Diskus	FLU	GSK	<5 μm	20–25	Medium/low	Constant	Multi-unit
Seretide Diskus	FLU	GSK	<5 μm	20–25	Medium/low	Constant	Multi-unit
Flixotide Diskhaler	FLU	GSK	<5 μm	25–30	Medium/low	Constant	Multi-unit
Rolenium Elpenhaler	FLU	Elpen	<5 μm	15–20	Medium/low	Constant	Single-unit
Pulmicort Turbuhaler	BUD	AstraZeneca	<5 μm	30–35	Medium/high	Increasing	Multi-unit
Symbicort Turbuhaler	BUD	AstraZeneca	<5 μm	45–50	Medium/high	Increasing	Multi-unit
Budelin Novolizer	BUD	Meda	<5 μm	40–45	Medium/low	Increasing	Multi-unit
Budesonide Easyhaler	BUD	Sandoz	<5 μm	20–25	Medium/low	Increasing	Multi-unit
Budesonide Clickhaler	BUD	Merck Generics	<5 μm	10–15	Medium/high	Slightly increasing	Multi-unit
Budesonide Cyclohaler	BUD	Teva Pharma	<5 μm	25–30	Low	Slightly increasing	Single-unit
Budesonide Jethaler	BUD	Ratiopharm	<5.1 μm	35–40	Medium/high	Increasing	Multi-unit
Foster NEXThaler	BDP	Chiesi	<5 μm	40–45	Medium/high	Constant	Multi-unit
Asmanex Twisthaler	MOM	Merck & Co	<5 μm	30–35 [51,52]	High	Slightly increasing	Multi-unit

FPF as percent of label claim, unless stated otherwise.
[a] Defined as: high (IFR at 4 kPa < 45 L/min), medium/high (IFR at 4 kPa between 45 and 60 L/min); medium/low (IFR at 4 kPa between 60 and 80 L/min) and low (IFR at 4 kPa > 80 L/min). BUD, budesonide; BDP, beclomethasone (dipropionate); DPI, dry powder inhaler; FLU, fluticasone (propionate); FPF, fine particle fraction; ICS, inhaled corticosteroid, IFR, inspiratory flow rate; MOM, mometasone (furoate).

drug particles or a mixture of drug particles with a micronised excipient. In both examples, the excipient is usually lactose, which is used to dilute the drug and improve the flow properties to assist reproducible dosing to the patient. Adhesive mixtures and pellet formulations consist initially of particles that are too large to penetrate to the target area. They have to be de-agglomerated or dispersed during inhalation to release the drug particles in the appropriate aerodynamic size range.

The energy for de-agglomeration is derived from the inhaled air stream. Well-designed inhalers transfer the kinetic energy of the airflow effectively into drag, inertial or frictional forces, which break down the pellet formulations into primary particles or detach drug particles from the carrier surface [30]. Optimal utilisation of the kinetic energy to generate de-agglomeration forces requires design features that largely determine the inhaler resistance to air flow. Such features can, for instance, be turbulent shear zones (creating drag and lift forces) or whirl and circulation chambers containing impact bodies. Inhalers with highly effective de-agglomeration principles are more likely to have a higher air flow resistance and provide greater lung deposition than those with a low internal resistance [16,37,50].

Table 1B Review of some bronchodilator (BD) delivering DPIs.

Inhaler	BD	Manufacturer	% FPF at 4 kPa		Resistance[a]	FPF as Fu(IFR)	Multi-/single-unit dose
			Defined as	% FPF			
Serevent Diskus	SAL	GSK	<5 μm	20–25	Medium/low	Slightly increasing	Multi-unit
Seretide Diskus	SAL	GSK	<5 μm	20–25	Medium/low	Constant	Multi-unit
Salbutamol Cyclohaler	SAL	Teva	<5 μm	25–30	Low	Increasing	Single-unit
Oxis Turbuhaler	FOR	AstraZeneca	<5.8 μm	35–40	Medium/high	Increasing	Multi-unit
Symbicort Turbuhaler	FOR	AstraZeneca	<5 μm	40–45	Medium/high	Increasing	Multi-unit
Formatris Novolizer	FOR	Meda	<5 μm	40–45	Medium/low	Increasing	Multi-unit
Rolenium Elpenhaler	FOR	Elpen	<5 μm	15–20	Medium/low	Constant	Single-unit
Foster NEXThaler	FOR	Chiesi	<5 μm	35–40	Medium/high	Constant	Multi-unit
Foradil Aerolizer	FOR	Merck & Co.	<5.8 μm	25–30 [53]	Low	Increasing	Single-unit
Onbrez Breezhaler	IND	Novartis	<5 μm	35–40	Low	Constant	Single-unit
Seebri Breezhaler	GB	Novartis	<5 μm	32–52 [54]	Low	Constant	Single-unit
Eklira Genuair	ACC	Almirall	<5 μm	35–40	Medium/low	Slightly increasing	Multi-unit
Spiriva HandiHaler	TIO	Boehringer I	<5 μm	15–20	High	Constant	Single-unit

FPF as percent of label claim unless stated otherwise.
[a] Defined as: high (IFR at 4 kPa < 45 L/min), medium high (IFR at 4 kPa between 45 and 60 L/min); medium low (IFR at 4 kPa between 60 and 80 L/min) and low (IFR at 4 kPa > 80 L/min). ACC, aclidinium (bromide); BD, bronchodilator; DPI, dry powder inhaler; FOR, formoterol (fumarate dihydrate); FPF, fine particle fraction; GB, glycopyrronium (bromide); IFR, inspiratory flow rate; IND: indacaterol (maleate); SAL, salmeterol (xinafoate); TIO, tiotropium (bromide).

Generally, effective utilisation of the available energy for de-agglomeration results in an increasing FPF with increasing IFR. The clinical relevance of the internal resistance of an inhaler refers not only to a higher proportion of FPF dose achieved at the same inspiratory effort and a compensating increase in FPF at higher IFR. Resistance also has an impact on the site of deposition of drug particles in the respiratory tract. High-resistance inhalers reduce the maximal attainable flow rate, which equals the quotient of the square root of the pressure drop achieved (given in $\sqrt{kPa}$) and the inhaler resistance (in $kPa^{0.5}$ min L^{-1}), thus reducing oropharyngeal deposition. Inhaling against a high resistance furthermore opens up the oropharynx and vocal cords, providing a wider passageway for the aerosol and increasing total lung dose [37].

Most inhalers deliver FPFs between 20% and 30% of the label claim at pressure drops between 2 and 4 kPa (Fig. 4A). For inhalers that deliver more or less the same amount of FPF over the entire range of attainable pressure drops (>2 kPa), higher pressure drops (corresponding with higher flow rates) are not desirable, because this is at the cost of total (in particular central and peripheral) lung deposition due to increased losses in the oropharynx at the higher flow rates. DPIs with IFR-independent FPF generation are frequently low-resistance devices, which facilitate the generation of higher IFRs. For instance, the increase in flow rate between 2 and 4 kPa through a high-resistance inhaler like the HandiHaler® is only from 28 to 39 L/min versus 57–106 L/min for the low-resistance Aerolizer®. In contrast, DPIs delivering a higher FPF with increasing IFR are frequently high-resistance devices. Fig. 4B compares the flow rates at which FPF <5 μm reaches the value of 25% of label claim for the inhalers presented in Fig. 4A. The difference is between 36.4 L/min for the medium/high-resistance Symbicort® Turbuhaler® and 82.2 L/min for the low-resistance Cyclohaler®. On the basis of the impaction parameter (based on flow rate) as predictor for inertial impaction, this might give a 2.25 times higher chance of oropharyngeal impaction for the same particle size for the low-resistance device. For the Diskus®, Clickhaler® and Elpenhaler® FPF values of 25% of label claim were not obtained at any flow rate with the devices used to produce Fig. 4A. Attaining a pressure drop of 2–4 kPa – which is sufficient to operate most inhalers successfully and results in clinically effective drug delivery – is easier when using a high-resistance inhaler than when using a low-resistance device, independent of the type and severity of the disease [13,31,50]. Even during exacerbations of asthma and COPD, patients are able to achieve the required pressure drop and the performance of an inhaler with a higher resistance is less influenced by the underlying degree of bronchoconstriction than with a low-resistance inhaler [31]. Also, young children and adult patients with severely impaired lung function generate sufficiently high pressure drops to enable them to use IFR-dependent higher resistance inhalers such as the Turbuhaler® and Novolizer® effectively [13,31].

The ideal dry powder inhaler?

Determining the best inhaler is dependent on the circumstances and characteristics of each patient, so may vary in different clinical settings. However, based on the considerations discussed above and balancing the requirements of a broad range of patients, the ideal DPI device would have the following characteristics: a high and consistent IFR-dependent FPF (contributing to consistent central and peripheral lung deposition regardless of IFR) and a medium to high internal resistance to limit the IFR and minimise loss of the FPF dose in the oropharynx. In addition, the inhaler should be easy for patients to learn and maintain correct usage and small enough to be convenient to carry around or store, to minimise incorrect use and maximise adherence to the therapy [16]. Table 1 shows how some of the widely used inhalers measure up to these requirements. Originator devices like the Turbuhaler® and Novolizer® deliver a high FPF (1–3 μm) to the central and peripheral airways, where the medication being delivered (either bronchodilator or anti-inflammatory ICS) is generally most needed, up to 40% or more of the label claim at the flow rate corresponding with 6 kPa [29,30,33,43–46]. In contrast, some generic inhalers like the Elpenhaler® deliver more or less the same low FPF of <20% at all flow rates.

Conclusions

There are a growing number of dry powder inhalers available and these differ greatly in their design, technical characteristics and other individual features. Some inhalers have characteristics that mean they are likely to work for a variety of patients, which may provide a certain level of convenience for physicians. However, there are many factors to consider when selecting the optimal inhaler for patients with asthma or COPD. Apart from the type of drug inside the inhaler, the level of clinical evidence for its efficacy and safety, doctor and patient preferences, the technical characteristics of the different inhalers and the delivery and deposition of the fine particle dose to the lungs may be important additional considerations to help the physician to select the most appropriate device for the individual patient to optimise their treatment.

Conflict of interest statements

Pascal Demoly is a consultant and a speaker for Stallergenes, ALK, Circassia and Chiesi and was a speaker for Merck, AstraZeneca, Menarini and GlaxoSmithKline.

Paul Hagedoorn receives royalties from Almirall and Meda (Genuair and Novolizer sales) and is a speaker for AstraZeneca.

Anne de Boer receives royalties from Almirall and Meda (Genuair and Novolizer sales) and is a speaker for AstraZeneca.

Henderik W. Frijlink's employer has a royalty agreement regarding the Novolizer and the Genuair and he has been a speaker for AstraZeneca and Meda.

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References

[1] Global Initiative for Asthma (GINA). Global strategy for asthma prevention and management [cited 2013 Aug 20]; Available from: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf; 2012.

[2] Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005;127:335—71.

[3] Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. Lancet 2011;377:1032—45.

[4] Aerosol Drug Management Improvement Team (ADMIT). The ADMIT webpage [cited 2013 Aug 20]; Available from: http://www.admit-online.info/en/; 2013.

[5] Vincken W, Dekhuijzen PR, Barnes P. The ADMIT series — issues in inhalation therapy. 4) How to choose inhaler devices for the treatment of COPD. Prim Care Respir J — J Gen Pract Airw Group 2010;19:10—20.

[6] Denyer J, Nikander K, Smith NJ. Adaptive aerosol delivery (AAD) technology. Expert Opin Drug Deliv 2004;1:165—76.

[7] Fischer A, Stegemann J, Scheuch G, Siekmeier R. Novel devices for individualized controlled inhalation can optimize aerosol therapy in efficacy, patient care and power of clinical trials. Eur J Med Res 2009;14(Suppl. 4):71—7.

[8] Anderson P. Use of Respimat Soft Mist inhaler in COPD patients. Int J Chron Obstruct Pulmon Dis 2006;1:251—9.

[9] Adcock IM, Caramori G, Kirkham PA. Strategies for improving the efficacy and therapeutic ratio of glucocorticoids. Curr Opin Pharmacol 2012;12:246—51.

[10] Chrystyn H, Niederlaender C. The Genuair(R) inhaler: a novel, multidose dry powder inhaler. Int J Clin Pract 2012;66:309—17.

[11] Andrzej E, Malgorzata BE. Easyhaler — ideal dry powder inhaler. Pol Merkur Lekarski — Organ Pol Tow Lek 2010;28:307—10.

[12] Abdelrahim ME. Emitted dose and lung deposition of inhaled terbutaline from Turbuhaler at different conditions. Respir Med 2010;104:682—9.

[13] Selroos O, Borgstrom L, Ingelf J. Performance of Turbuhaler(R) in patients with acute airway obstruction and COPD, and in children with asthma : understanding the clinical importance of adequate peak inspiratory flow, high lung deposition, and low in vivo dose variability. Treat Respir Med 2006;5:305—15.

[14] Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH. Technological and practical challenges of dry powder inhalers and formulations. Adv Drug Deliv Rev; 2014. http://dx.doi.org/10.1016/j.addr.2014.04.004.

[15] Azouz W, Chrystyn H. Clarifying the dilemmas about inhalation techniques for dry powder inhalers: integrating science with clinical practice. Prim Care Respir J — J Gen Pract Airw Group 2012;21:208—13.

[16] Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. Prim Care Respir J — J Gen Pract Airw Group 2009;18:243—9.

[17] Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med 2008;102:593—604.

[18] Self TH, Wallace JL, George CM, Howard-Thompson A, Schrock SD. Inhalation therapy: help patients avoid these mistakes. J Fam Pract 2011;60:714—21.

[19] van der Palen J, van der Valk P, Goosens M, Groothuis-Oudshoorn K, Brusse-Keizer M. A randomised cross-over trial investigating the ease of use and preference of two dry powder inhalers in patients with asthma or chronic obstructive pulmonary disease. Expert Opin Drug Deliv 2013;10:1171—8.

[20] Hodder R, Reese PR, Slaton T. Asthma patients prefer Respimat Soft Mist inhaler to Turbuhaler. Int J Chron Obstruct Pulmon Dis 2009;4:225—32.

[21] Welch MJ, Nelson HS, Shapiro G, Bensch GW, Sokol WN, Smith JA, et al. Comparison of patient preference and ease of teaching inhaler technique for Pulmicort Turbuhaler versus pressurized metered-dose inhalers. J Aerosol Med — Off J Int Soc Aerosols Med 2004;17:129—39.

[22] Sheth K, Bernstein JA, Lincourt WR, Merchant KK, Edwards LD, Crim CC, et al. Patient perceptions of an inhaled asthma medication administered as an inhalation powder via the Diskus or as an inhalation aerosol via a metered-dose inhaler. Ann Allergy Asthma Immunol — Off Publ Am Coll Allergy Asthma Immunol 2003;91:55—60.

[23] Price D, Lee AJ, Sims EJ, Kemp L, Hillyer EV, Chisholm A, et al. Characteristics of patients preferring once-daily controller therapy for asthma and COPD: a retrospective cohort study. Prim Care Respir J — J Gen Pract Airw Group 2013;22:161—8.

[24] Chrystyn H. Do patients show the same level of adherence with all dry powder inhalers? Int J Clin Pract Suppl; 2005:19—25.

[25] Thomas M, Price D, Chrystyn H, Lloyd A, Williams AE, von Ziegenweidt J. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. BMC Pulm Med 2009;9:1.

[26] Thomas M, Williams AE. Are outcomes the same with all dry powder inhalers? Int J Clin Pract Suppl; 2005:33—5.

[27] Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess 2001;5:1—149.

[28] Hickey AJ, Martonen TB, Yang Y. Theoretical relationship of lung deposition to the fine particle fraction of inhalation aerosols. Pharm Acta Helv 1996;71:185—90.

[29] Frijlink HW, De Boer AH. Dry powder inhalers for pulmonary drug delivery. Expert Opin Drug Deliv 2004;1:67—86.

[30] de Boer AH, Hagedoorn P, Gjaltema D, Goede J, Frijlink HW. Air classifier technology (ACT) in dry powder inhalation part 4. Performance of air classifier technology in the Novolizer multi-dose dry powder inhaler. Int J Pharm 2006;310:81—9.

[31] Borgstrom L. On the use of dry powder inhalers in situations perceived as constrained. J Aerosol Med — Off J Int Soc Aerosols Med 2001;14:281—7.

[32] Agertoft L, Pedersen S. Lung deposition and systemic availability of fluticasone Diskus and budesonide Turbuhaler in children. Am J Respir Crit Care Med 2003;168:779—82.

[33] Newman SP. Aerosol deposition considerations in inhalation therapy. Chest 1985;88:152S—60S.

[34] Frijlink HW, de Boer AH. Trends in the technology-driven development of new inhalation devices. Drug Discov Today Technol 2005;2:47—57.

[35] Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med 2005;172:1497—504.

[36] Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, et al. Scintigraphic comparison of budesonide

deposition from two dry powder inhalers. Eur Respir J 2000; 16:178—83.
[37] Ehtezazi T, Horsfield MA, Barry PW, O'Callaghan C. Dynamic change of the upper airway during inhalation via aerosol delivery devices. J Aerosol Med — Off J Int Soc Aerosols Med 2004;17:325—34.
[38] Barnes PJ. Distribution of receptor targets in the lung. Proc Am Thorac Soc 2004;1:345—51.
[39] White MV. Muscarinic receptors in human airways. J Allergy Clin Immunol 1995;95:1065—8.
[40] Meurs H, Dekkers BG, Maarsingh H, Halayko AJ, Zaagsma J, Gosens R. Muscarinic receptors on airway mesenchymal cells: novel findings for an ancient target. Pulm Pharmacol Ther 2013;26:145—55.
[41] Pera T, Zuidhof A, Valadas J, Smit M, Schoemaker RG, Gosens R, et al. Tiotropium inhibits pulmonary inflammation and remodelling in a guinea pig model of COPD. Eur Respir J 2011;38:789—96.
[42] Milara J, Serrano A, Peiro T, Gavalda A, Miralpeix M, Morcillo EJ, et al. Aclidinium inhibits human lung fibroblast to myofibroblast transition. Thorax 2012;67:229—37.
[43] Asking L, Maayan C, Petterson G. Flutide Diskus less consistent than Pulmicort Turbuhaler with respect to in vitro fine particle dose proportionality. Am J Respir Crit Care Med 2009;163:A441.
[44] Thorsson L, Edsbacker S, Kallen A, Lofdahl CG. Pharmacokinetics and systemic activity of fluticasone via Diskus and pMDI, and of budesonide via Turbuhaler. Br J Clin Pharmacol 2001;52:529—38.
[45] Bisgaard H, Klug B, Sumby BS, Burnell PK. Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. Eur Respir J 1998;11:1111—5.
[46] Borgstrom L, Asking L, Thorsson L. Idealhalers or realhalers? A comparison of Diskus and Turbuhaler. Int J Clin Pract 2005; 59:1488—95.
[47] DeHaan WH, Finlay WH. Predicting extrathoracic deposition from dry powder inhalers. J Aerosol Sci 2004;35:309—31.
[48] Kohler D. The Novolizer: overcoming inherent problems of dry powder inhalers. Respir Med 2004;98(Suppl. A):S17—21.
[49] Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J 2011; 37:1308—31.
[50] de Koning JP. Dry powder inhalation: technical and physiological aspects, prescribing and use: chapter 2: effect of resistance to airflow on the inspiratory flow curve. Groningen, The Netherlands: University of Groningen; 2001.
[51] Kondo T, Tanigaki T, Tazaki G, Wanatabe H, Ishii H, Tsunoda T, et al. Areguri 2010;59:950—5.
[52] Yang TT, Li S, Wyka B, Kenyon D. Drug delivery performance of the mometasone furoate dry powder inhaler. J Aerosol Med 2001;14:487—94.
[53] Weuthen T, Roeder S, Brand P, Müllinger B, Scheuch G. In vitro testing of two formoterol dry powder inhalers at different flow rates. J Aerosol Med 2002;15:292—303.
[54] Therapeutic Goods Administration. In: Department of Health & Ageing, editor. Australian public assessment report for glycopyrronium (as bromide); 2013.